JAMA Clinical Guidelines Synopsis

Antithrombotic Therapy for Venous Thromboembolic Disease

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GUIDELINE TITLE Antithrombotic Therapy for Venous Thromboembolic Disease

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PREVIOUS GUIDELINE 2012

DEVELOPER American College of Chest Physicians (ACCP)

FUNDING SOURCE ACCP

TARGET POPULATION Patients with deep venous thrombosis (DVT) of the leg or pulmonary embolism (PE)

MAJOR RECOMMENDATIONS

- In patients without cancer and lower extremity DVT or PE, anticoagulation with dabigatran, rivaroxaban, apixaban, or edoxaban is preferred over vitamin K antagonist (VKA) therapy (grade 2B).
- In patients with cancer and DVT or PE (cancer-associated thrombosis), low-molecular-weight heparin (LMWH) is preferred over VKA therapy, dabigatran, rivaroxaban, apixaban, or edoxaban (grade 2C).
- In patients with an unprovoked DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, aspirin therapy is suggested (grade 2B).
- In patients with low-risk PE and adequate home circumstances, treatment at home or brief hospitalization (vs traditional 5 days of inpatient treatment) is suggested (grade 2B).
- In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a low risk of recurrent venous thromboembolism (VTE; not hospitalized, normal mobility, no active cancer, and presence of reversible risk factor), clinical surveillance is suggested over anticoagulation (grade 2C). In similar patients without these markers of low risk, anticoagulation is suggested (grade 2C).

Summary of the Clinical Problem

The estimated annual incidence of VTE, defined as DVT of the leg or PE, ranges from 104 to 183 per 100 000 person-years.[1] Compared with those without VTE, the 30-year mortality risk is increased for survivors of an episode of VTE and for survivors of an episode of PE (64 vs 136 and 211 per 1000 person-years, respectively).[2] In 2012, the ACCP released the ninth-edition guidelines for antithrombotic therapy and prevention of thrombosis.[3] Since the publication of that guideline, there has been improved understanding of the diagnosis and prognosis of VTE. The addition of non–vitamin K oral anticoagulants (NOACs) has altered the landscape of treatment options. This update addresses the role for NOACs and provides new recommendations for management of subsegmental PE and treatment of cancer-associated VTE.

Characteristics of the Guideline Source

This statement was funded by the ACCP (**Table**). An oversight committee at *Chest* appointed an editor for this guideline who nominated the members of the writing group. Panelists were required to disclose any potential conflicts of interest (COIs),[4] which were classified as primary or secondary; panelists with primary COIs were required to abstain from voting on related topic areas but could participate in discussions provided they refrained from strong advocacy. Of the topics reviewed for this synopsis, those relating to use of NOACs in patients with VTE without cancer and to use of LMWH in patients with VTE with cancer were notable for more serious COIs among the majority of panelists.

Evidence Base

A literature search was conducted for articles published between 1946 and July 2015. The quality of identified systematic reviews was assessed using a validated tool. Prospective cohort studies were included in the search when identified randomized trials were deemed inadequate. Meta-analyses were performed on the pooled data. Selected studies were assessed for risk of bias using the Cochrane Risk of Bias Tool.[5] The quality of evidence and strength of recommendations were categorized using the GRADE approach.[6] External peer review was conducted after panel consensus was achieved on the drafted recommendations and before publication of the guidelines. No public commentary was obtained.

Benefits and Harms

In patients without cancer and VTE, NOACs are preferred over VKAs for anticoagulant therapy (grade 2B). This preference is based on data demonstrating that the risk reduction for long-term recurrent VTE

Table. Guideline Rating

Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the guideline development group	Fair
Guideline development group composition	Good
Clinical practice guideline–systematic review intersection	Good
Establishing evidence foundations and rating strength for each of the guideline recommendations	Good
Articulation of recommendations	Good
External review	Fair
Updating	Good
Implementation issues	Good

with dabigatran, rivaroxaban, apixaban, or edoxaban is similar to the risk reduction with VKAs, while the risk of bleeding is generally less with NOACs than with VKAs.

In patients with cancer-associated thrombosis (VTE and cancer), LMWH is preferred over VKAs for long-term anticoagulant therapy (grade 2C). This preference is based on a meta-analysis of 9 randomized trials comparing LMWH with VKAs or NOACs with VKAs suggesting that LMWH was more effective than NOACs in cancer-associated thrombosis (grade 2C); however, this finding may be attributed to differences among study populations and design.[7]

In patients with creatinine clearance below 30 mL/min, VKA therapy is preferred, as most NOACs and LMWH are contraindicated in the setting of severe renal impairment.

NOACs provide greater convenience for patients than VKAs because these drugs do not require international normalized ratio monitoring. However, higher pricing may limit access and adherence to NOACs. Furthermore, dabigatran may increase risk of acute coronary syndromes in some populations.[8]

Aspirin is likely less effective than anticoagulant therapy for preventing recurrent VTE. In patients with unprovoked VTE who discontinue anticoagulant therapy after a 3-month treatment course and who are not at increased bleeding risk, a pooled analysis suggests that extended treatment with aspirin is associated with reduced risk of recurrent VTE vs placebo, with an absolute risk reduction of 5.3% and a hazard ratio of 0.65 (95% CI, 0.49-0.86). An increased risk of bleeding associated with aspirin use is not statistically significant (hazard ratio, 1.31; 95% CI, 0.48-3.53).[3] The authors of the guideline do not specify a recommended aspirin dosage, but 100 mg/d is suggested based on a 2014 meta-analysis.[9]

Outpatient anticoagulant therapy is suggested over hospitalization in patients with acute PE if a patient feels well enough to be treated at home (grade 2B). The authors suggest that this strategy should be limited to low-risk patients who are clinically stable; have good cardiopulmonary reserve; have no serious comorbidities such as recent bleeding, severe renal or liver disease, or severe thrombocytopenia; and are likely to adhere to anticoagulant therapy. Inpatient treatment is indicated for patients with evidence of right ventricular dysfunction or elevated cardiac biomarkers.

The authors of the guideline did not identify any randomized trials of patients with isolated subsegmental PE. In a number of small retrospective analyses of patients with isolated subsegmental PE and no proximal DVT who were not receiving anticoagulant therapy, no episodes of recurrent VTE were observed. These data led the guideline authors to suggest that in similar patients who are at low risk of recurrent VTE (defined as not being hospitalized, not having reduced mobility, not having active cancer, and having a reversible risk factor for DVT), surveillance for proximal DVT with serial duplex imaging is suggested over anticoagulant therapy. In patients with isolated subsegmental PE who have poor cardiopulmonary reserve, decreased mobility, active cancer, or irreversible VTE risk factors, anticoagulant therapy is favored over surveillance.

Discussion

Treatment of VTE has changed markedly over the last 4 years with the advent of NOACs. Concurrent with greater use of highly sensitive computed tomographic pulmonary angiography in the diagnosis of VTE, the incidence of PE has increased by 81%, from 62.3 to 112.3 per 100 000 US adults between 1998 and 2006, with up to 15% of PE diagnoses now being attributed to isolated subsegmental PE. Among patients with isolated subsegmental PE, 7% may experience a major bleeding episode during treatment.[10] Retrospective analyses suggest that the risk of recurrent VTE may be very low, estimated at 0% (95% CI, 0%-7.4%).[10] This guideline is the first to make recommendations that take these changes into account.

Areas in Need of Future Study or Ongoing Research

While a variety of patient-specific factors may guide selection of specific anticoagulants for long-term treatment of VTE, comparative effectiveness studies are needed to identify whether any specific NOACs provide superior risk reduction for recurrent VTE or whether specific drugs are most effective in specific circumstances. Similar studies are also needed to directly compare the effectiveness of NOACs and LMWH in the treatment of cancer-associated thrombosis. NOACs, if found to be noninferior or superior to LMWH, would provide an alternate treatment for patients who prefer to avoid injecting LMWH. Finally, randomized clinical trials are needed to define the utility of antithrombotic treatment for isolated subsegmental PE.

Related Guidelines and Other Resources

Institute for Clinical Systems Improvement Health Care Guideline: Venous Thromboembolism Diagnosis and Treatment (January 2013)

ARTICLE INFORMATION

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